| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/802,520 | LAL ET AL. | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant amends claim 1 to add items 1(b-d) and amends claim 2(c).

Since applicant has elected in paper Nos: 8 and 12, Group I, claims 1-6, drawn to a nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding SEQ ID NO:1, species the fragment of SEQ ID NO:3, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claims 1( b-d) directed to a nucleic acid sequence encoding an antigenic epitope of SEQ ID NO:1, from about amino acid residue G59 to about amino acid residue D75, and from about amino acid residue S455 to amino acid residue T478 of SEQ ID NO:1, a nucleic acid sequence encoding a biological active fragment of SEQ ID NO:1, from about amino acid residue T32 to the amino acid residue L136, or a nucleic acid sequence encoding a naturally occurring variant of SEQ D NO:1, and claim 2(c ), directed to a variant of SEQ ID NO:2, have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03. Newly submitted claims 1(b-c) and 2(c ) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

A nucleic acid sequence encoding an antigenic epitope of SEQ ID NO:1, from about amino acid residue G59 to about amino acid residue D75, and from about amino acid residue S455 to amino acid residue T478 of SEQ ID NO:1, or a biological active

fragment of SEQ ID NO:1, from about amino acid residue T32 to the amino acid residue L136 are structurally distinct from the elected species fragment of SEQ ID NO:3.

Further, a polynucleotide encoding a naturally occurring variant of SEQ D NO:1, and a variant of SEQ ID NO:2 are structurally distinct from SEQ ID NO:2, and belong to group II, directed to variants of SEQ ID NO:2, including SEQ ID NO:10, as recited in the Office action of paper No:7.

Accordingly, claims 1(a), 2(a-b), 3-6, SEQ ID NO:2, and a nucleic acid sequence encoding the predicted SEQ ID NO:1, and a fragment of SEQ ID No:2, i.e. SEQ ID No: 3 are examined in the instant application. It is noted that variants of SEQ ID NO:2 in claims 1(d) and 2(c), including SEQ ID NO:10 has been withdrawn from consideration as being drawn to non-elected invention. It is further noted that amended 1(b-c), drawn to fragments of SEQ ID NO:2 is withdrawn from consideration as being drawn to non-elected species.

This application contains claims drawn to an invention nonelected with traverse in Paper Nos.8, 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

**REJECTION UNDER 35 USC 101, UTILITY**

Claims 1(a), 2(a-b), 3-6 remain rejected under 35 USC 101, pertaining to lack of a specific, and substantial utility or a well established utility for reasons already of record in paper No: 13.

Applicant recites legal standards on pages 5-6.

Applicant asserts that knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit.

Applicant further asserts that SEQ ID No:1, encoded by SEQ ID NO:2 was identified as a STEAP related protein by a combination of criteria: 1) Sequence homology and structural features, e.g. transmembrane domains, shared between SEQ ID NO:1 and STEAP, 2) Prostate-specific expression of SEQ ID NO:1 (Table 1), and 3) Over-expression of SEQ ID NO:1 in prostate hyperplasia and prostate cancer (Table 2) and in prostate tumor cell line modeling human prostate cancer (Table 3). All of these properties are shared by the STEAP protein described by Hubert et al.

Applicant asserts that SEQ ID NO:1 and STEAP protein share more than 40% identity over 490 amino acids, and this is more than enough homology to demonstrate a reasonable probability that the utility of STEAP can be imputed to the claimed invention, since it is well known in the art that the probability that two unrelated polypeptide share more than 40% homology over 70 amino acid residues is exceedingly small, as taught by Brenner et al. Applicant asserts that none of the references cited by the Examiner contradict Brenner's basic rule that sequence homology in excess of 40% homology over 70 amino acid residues yields a high probability of functional homology, nor do they contradict the evidence that the predicted transmembrane domains shared by the two proteins indicate the lilkelihood that SEQ ID NO:1, like STEAP, is a cell surface antigen.

Applicant submits the alignment of SEQ ID NO:1 with STAMP1, described by Kormaz et al, recently published in 2002, and asserts that the reference by Kormaz et al independently confirms the identity of SEQ ID NO:1 as a STEAP related protein.

Applicant asserts that the data reflect the prostate-specific expression of SEQ ID NO:1 (Table 1), and over-expression of SEQ ID NO:1 in prostate hyperplasia and prostate cancer (Table 2), and that none of this evidence is refuted by the Examiner.

Applicant asserts that none of the references recited by the Examiner specifically address the well known use of prostate cell lines derived from prostate cancers in modeling human prostate cancer. Applicant recites Rothermund et al, and Denmeade et al, which teach the use of the LNCaP cell line in studying the expression of gene associated with prostate cancer. Kormaz et al also describes the use of the LNCaP cell line in studying the overexpression of STAMP1 protein in prostate cancer. Applicant asserts that if the use of prostate cell lines were generally of such inconsequential value, as suggested by the Examiner, the evaluation of potential therapeutic agents for cancer treatment would require far more hazardous clinical studies at an earlier stage with a much higher risk for failure. Applicant asserts that no such clinical studies are required for patentability.

The recitation of the legal standards, and of the references by Brenner et al, Kormaz et al, Rothermund et al, and Denmeade et al is acknowledged.

Applicant's arguments in paper No: 14 have been considered but are found not to be persuasive for the following reasons:

It is noted that the specification does not disclose any actual biological activity of the predicted encoded SEQ ID NO:1, nor any data confirming that the portion extending from T32 to L136 of SEQ ID NO:1, which is claimed to be similar to a KNT NAD-binding domain (specification, p.10, lines 22) actually has any biological activity, nor any consensus sequence required for the activity of the encoded protein or for the identification of a STEAP protein.

The three criteria recited by Applicant to assert the utility of SEQ ID NO:2 which putatively encodes SEQ ID NO:1 are not convincing for the following reasons: 1) One cannot determine that SEQ ID NO:2, and its putative encoded SEQ ID NO:1 would have the same function and properties as STEAP or STAMP1 based solely on sequence homology and sharing some structural features, e.g. transmembrane domains, 2) The data showing over-expression of SEQ ID NO:1 in prostate hyperplasia and prostate cancer (Table 2) and in prostate tumor cell lines (Table 3) seems to be derived from electronic Northern which is based on non-representative libraries, and thus are not reliable.

Concerning sequence homology, although Applicant discloses 40% identity over 490 amino acids between STEAP protein and the predicted encoded SEQ ID NO:1, this is not persuasive because the relevance of the apparently arbitrarily chosen regions of identity is unclear since there is no suggestion, either in the specification or the art of record that any of these regions have been implicated in any particular function and it would appear, if meaningful at all, that the similarities in these regions may be involved with as yet undefined biochemical properties and functions. Concerning homology in the

six transmembrane region, this homology at most indicates that the putative SEQ ID NO:1 is a surface antigen, a property shared by a family of six membrane proteins, which has not been shown to share the same function or has common utility. Based on the information in the art or record and in the specification, the functions of those claimed domains are unknown and no particular function of SEQ ID NO:1 can be ascribed to it based on sequence identity to the prior art proteins. Although it is clear that methods are available to identify proteins with identity between primary amino acid sequences, it is well known and clearly understood in the art, as taught by Bowie et al that prediction of protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex and unpredictable, and it is also well known in the art, as exemplified by Lazar et al and Burgess et al that even a single amino acid change can alter protein function. The unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is further demonstrated by Bork and Scott et al . Bork teaches the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality. The teaching of Scott et al further confirm the teaching of Bork, wherein Scott et al teach an example of misidentification of the function of a protein based on homology alone, and conclude that it is important to

confirm the function of a newly identified gene products even when the database reveal significant homology to proteins of known function.

Concerning the 99% similarity between the predicted SEQ ID NO:1 and the recently published STAMP1 by Korkmaz et al, 2002, which belongs to a different subfamily of six transmembrane family than STEAP (Korkmaz et al, p. 36690, second column, third paragraph), as shown in the alignment of Exhibit B, submitted in the response, the function of STAMP1 is not known, and one cannot predict that SEQ ID NO:1 has the same function as STAMP 1, based on sequence homology alone, as taught by Bowie et al, and Scott et al, and because as exemplified by Lazar et al and Burgess et al, even a single amino acid change can alter protein function..

Thus, in view of the information known in the art, it could not be predicted that a determination of a function of the predicted encoded SEQ ID NO:1 could be made based on sequence data alone. Further, given the differences between the predicted SEQ ID NO:1 and the prior art proteins, and given the unpredictability known in the art as evidenced by Bowie et al, Lazar et al and Burgess et al, as well as the unpredictability of the art of comparative sequence analysis to discern protein function from structure as taught by Bork, and Scott et al, sequence identity alone cannot give a reasonable correlation between the structure and function of the predicted SEQ ID NO:1 and the disclosed prior art proteins.

Further, even if SEQ ID NO:1 is STAMP-1 like, and although STAMP-1 is overexpressed in prostate cancer tissues as compared with normal tissue, one cannot predict that SEQ ID NO:2 and polynucleotides encoding SEQ ID NO:1 also overexpress

in prostate cancer tissues as compared to normal tissues, because different sequences express independently of each other. Moreover, even if SEQ ID NO:2 is a variant of STAMP-1, one cannot predict that SEQ ID NO:2 and polynucleotides encoding SEQ ID NO:1 also overexpress in prostate cancer tissues as compared to normal tissues, because it is well known in the art that variants are not always expressed in the same pattern as the wild type parent sequence. For example, Schmid S et al, 2001, J comparative Neurology, 430(2): 160-71, teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996, Mol Brain Res, 42: 1-17, teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

Moreover, the data showing over-expression of SEQ ID NO:1 in prostate hyperplasia and prostate cancer (Table 2) and in prostate tumor cell lines (Table 3) seems to be derived from electronic Northern (specification pages 28 and page 33, first paragraph) which are based on non-representative libraries, and thus are not reliable. The electronic Northern findings do not confer utility on SEQ ID NO:2. It is known in the art that the cDNA libraries used for the electronic Northerns are made up of a

"representative" population of clones which are isolated and sequenced from a library source. It is noted that the representative population of the Incyte transcript libraries in Table 2 are from 1157 to 8829. However, the Examiner takes note that cells in the human body encode approximately 100,000 genes of which between 10,000 and 20,000 are thought to be expressed as mRNAs. It is clear that not all of the genes expressed as mRNAs are represented in the libraries in the claimed invention. The identification of SEQ ID NO:2 in the selected, incomplete libraries appears to be a serendipitous event.. The fact that the claimed polynucleotide is not expressed in one library or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is expressed in the tissue "represented" by the library. It is not possible to determine from the information in the specification whether SEQ ID NO:2 could be useful in cancer research or as a marker for cancer cells without further research on the material itself.

Concerning the use of the prostate cancer cell line LNCaP for studying expression of various genes, there is no indication that the prostate cancer cell line LNCaP is an art accepted model for prostate cancer, especially in view of the well known cell culture artifacts, wherein expression of a gene could be altered by cell culture conditions, as taught by Drexler et al, Embleton et al, Hsu et al, Freshney et al, and Dermer et al.

Concerning prostate specific expression of SEQ ID NO:2, as shown in Table 1, its utilities based solely on prostate specific property are shared by other unrelated prostate specific molecules, and thus are not specific.

For reasons set forth above and in previous Office action, claims 1(a), 2(a-b), 3-6 remain rejected for lack of a specific, substantial utility or well established utility.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT**

Claims 1(a), 2(a-b), 3-6 remain rejected under 112, first paragraph, enablment due to lack of a specific, substantial utility or a well established utility for reasons already of record.

The same arguments and reasons for rejection as set forth under 101 rejection apply here as well.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE**

Rejection under 35 USC 112, first paragraph of claims 1(a), 3-6 pertaining to lack of enablement for a polynucleotide "encoding" the polypeptide of SEQ ID NO:1, and a method of making said polypeptide remains for reasons already of record.

Applicant asserts as follows: While steady state mRNA levels are not always directly proportional to the amount of protein in a cell, mRNA levels are routinely used as an indicator of protein expression. Countless publications have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Applicant further asserts that the examples recited by the Office represent unusual mechanisms of gene regulation. Applicant recites a reference by Lewin B., stating that for most genes control at the stage of initiation, i.e. by the interaction of RNA polymerase with its promoter is a major control point and probably

the most common level of regulation. Applicant further asserts that one would be imprudent in assuming that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner.

The recitation of the reference by Lewin B. is acknowledged.

Applicant's arguments in paper No: 14 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the Lewin reference does not support Applicant's statement that mRNA levels are routinely used as an indicator of protein expression and that mRNA levels are usually a good indicator of protein levels in a cell, because the Lewin reference does not disclose a correlation between the levels of mRNA and protein expression. It only discloses that most genes control at the stage of initiation i.e. by the interaction of RNA polymerase with its promoter, initiation is a major control point and probably the most common level of regulation.

It is further noted that the Examiner did not recite that the levels of SEQ ID NO:1 are controlled predominantly in a post-transcriptional manner.

Further, the claimed polynucleotide of SEQ ID NO:2 and the putative encoded polypeptide of SEQ ID NO:1 lacks a specific, substantial or well established utility, *supra* (see rejection under 101, utility above).

In addition, it is unpredictable that SEQ ID NO:1, which is a deduced amino sequence from the polynucleotide of SEQ ID NO:2, is expressed in disease tissues in nature and /or overexpressed in disease tissues as compared to normal tissues. The references by Alberts et al, Shantz et al, and Fu et al, Yokota et al, clearly indicate that

the presence of mRNA does not always dictate that such mRNAs are translated into proteins, and that the predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For example, the p53 protein levels of expression do not correlate with levels of p53 mRNAs, and the p53 protein could be undetectable in cells expressing abundant amount of wild type p53 mRNA (Fu et al, figure 3, and page 4396, second column, of record). Further, the intracellular half-life of ornithine decarboxylase is less than 1 hour, and the post-translational regulation of the degradation of said enzyme is depending on the level of polyamines (Shantz et al, page 110, first column, of record). In addition, the retinoblasma 115 KD protein is not detected in all nine cases of lung small celll carcinoma, with either normal or abnormal size of mRNA (Yokota et al, of record).

Moreover, concerning Applicant's assertion that the examples recited by the Office represent unusual mechanisms of gene regulation, the arguments are not persuasive, because although some of the genes studied in the cited publication include special structural elements responsible for the observed translational regulation, the recited references by the Examiner are only some of examples of negative translational regulation. It is well known in the art that both translational and post-translational control is an important step in the control of gene expression, and although in some cases translational control could be specific and requires some structural pecularities, it is not necessarily that the translational control require structural pecularities (Jansen M, 1995, Pediatric Res, 37(6): 681-686).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

May 13, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER